**REMARKS**

**Information Disclosure Statements**

With respect to item 3, on page 2 of the Office Action, concerning the missing references, Applicants had those references hand delivered to the Office on 6/12/2003, along with a further IDS, citing ref. nos. 170-200. The PTO-1449 forms which have not yet been initialed appear to be:

IDS dated 6/3/2002 - ref. nos. 111-121 and 136-146

IDS dated 1/31/2002 - ref. nos. 160-166

IDS dated 6/12/2003 - ref. nos. 170-200

Consideration of all the art and return of the initialed PTO-1449 forms is respectfully requested.

Applicants submit herewith a statement of related cases and respectfully request that the Examiner consider the related applications with respect to prosecution of the above application.

**Section 112, first paragraph - Claim 1**

Claims 1, 4-9, 12, 13, 34-36 and 38 are rejected under 35 USC Section 112, first paragraph as containing new subject matter in the phrase "without increase in overall adverse events, compared to therapy with gemcitabine alone."

This rejection of claims 1, 4-9, 12, 13, 34-36 and 38 is rendered moot by removal of the offending language from claim 1.

Reconsideration and withdrawal of the rejection is respectfully requested.

**Section 112, first paragraph - Claim 37**

Claim 37 is rejected under 35 USC Section 112, first paragraph as containing new subject matter with respect to methods where an anti-ErbB2 antibody and gemcitabine are co-administered, and where the effective amounts of the anti-ErbB2 antibody and gemcitabine are lower than if the two agents had been administered as single agents.

Applicants respectfully traverse the rejection.

Applicants submit that the skilled person reviewing the disclosure of the originally filed application would conclude that it described the invention in claim 37 wherein "the effective amount of the combination is lower than the sum of the effective amounts of the anti-ErbB2 antibody and the gemcitabine, when administered individually, as single agents." In particular, originally-filed claim 12, which depended on claim 1, recited "the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said chemotherapeutic agent, when administered individually, as single agents." Said combination in originally-filed claim 1 was "an anti-ErbB2 antibody and a **chemotherapeutic agent other than an anthracycline derivative**" (emphasis added). Page 17, line 15 specifically identifies the chemotherapeutic agent gemcitabine, which is not an anthracycline derivative. Hence, the skilled person would agree that the original disclosure provided support for the recitation in claim 37 noted above, given that gemcitabine was explicitly identified as a chemotherapeutic agent other than an anthracycline derivative, and claim 12 concerned chemotherapeutic agents other than anthracycline derivatives.

Further support for the above-noted recitation in claim 37 can be found on page 5, lines 13-17 which states "The present invention...is based on the recognition that while treatment with anti-ErbB2 antibodies **markedly enhances the clinical benefit of the use of chemotherapeutic agents in general**, a syndrome of myocardial dysfunction has been observed that is a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies." (Emphasis added). As noted above, gemcitabine is identified on page 17, line 15, as a chemotherapeutic agent (other than an anthracycline derivative). The enhanced clinical benefit of chemotherapeutic agents **in general** (other than anthracycline derivatives), was claimed in claim 12 of the originally filed application. Hence, this further demonstrates that the recitation in claim 37 was fully supported by the originally filed disclosure.

The Examiner urges that the specification lacks even one example for the general concept of synergism. Applicants respectfully submit that the Example actually taught that assessments of time to disease progression (TTP in months) and response rates (RR) showed "a significant augmentation of the chemotherapeutic effect by HERCEPTIN®" (page 47, lines 2-3). This statement was not limited to the exemplified chemotherapeutic agents - paclitaxel, anthracycline and cyclophosphamide - but was intended to refer to chemotherapeutic agents in general. See, also, page 5, lines 14-15 "treatment with anti-ErbB2 antibodies markedly enhances the clinical benefit of the use of chemotherapeutic agents **in general**" (emphasis added). Gemcitabine was described in the general description as such a chemotherapeutic agent (page 17, line 15).

Moreover, Applicants note that the law is well established that Section 112, first paragraph does not require a working example. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). See, also, MPEP 2164.02. While Applicants acknowledge that there is no working example for the anti-ErbB2 and gemcitabine combination claimed herein, as explained above, Applicants submit that the skilled practitioner reviewing the disclosure of the originally filed application would have concluded that the presently claimed combination, and the augmentation/synergy recitation, set forth in claim 37 was described in the originally filed application in a manner that satisfied the requirements of 35 USC Section 112, first paragraph.

Reconsideration and withdrawal of the rejection of claim 37 is respectfully requested.

**Section 112, second paragraph**

Claims 1, 4-9, 12, 13, 34-36 and 38 are rejected under 35 USC Section 112, second paragraph as being indefinite. The scope of the phrase "overall

increase in adverse events" in claim 1 is considered to be unclear.

This rejection is rendered moot by removal of the offending language from claim 1.

Reconsideration and withdrawal of the rejection is respectfully requested.

Respectfully submitted,
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